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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Mangano

Serial No.: 09/426,792

Group Art Unit: 1614

Filed: October 22, 1999

Examiner: Spivack, Phyllis G.

For: METHODS FOR REDUCING MORTALITY AND MORBIDITY BY POSTOPERATIVE ADMINISTRATION OF A PHARMACOLOGIC CARDIOVASCULAR AGENT

Attorney Docket No.: 9114-004-999

RESPONSE UNDER 37 C.F.R. §1.111

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants have carefully considered the non-final Office Action, mailed July 12, 2002, in connection with the above-captioned application. Reconsideration of the claims in light of the remarks that follow is respectfully requested. Enclosed herewith are Exhibit A (Claim Amendments: Pending Claims) and a Petition for Extension of Time.

I. RESTRICTION REQUIREMENT

Applicants re-affirm their election of Group I, directed to administration of cardiovascular agents that are β_1 -adrenergic selective blockers to reduce cardiovascular disease complications following surgery under defined conditions. The new Claims (53-55) have been renumbered, and Claims 7-12 stand withdrawn from consideration by the PTO. Claims 1-6, 13-16, 49-51 and 53-55 are currently pending and under consideration. For the Examiner's convenience, the pending claims are attached at Exhibit A.

II. THE REJECTION UNDER 35. U.S.C. §103(a)

Claims 1-6, 13-16 and 49-55 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Goldstein, *et al.*, 1993, *J. Cardiovasc. Pharmacology* 22: 253-58 (hereinafter

'Goldstein') in view of Kataria, *et al.*, 1990, *J. Cardiothoracic Anesth.* 4/5 Suppl. 2: 13-16 (hereinafter 'Kataria'). Applicants respectfully submit that the PTO has not met its initial burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); MPEP § 2142. In particular, Applicants submit that neither Goldstein nor Kataria teach or suggest each and every element of the rejected claims.

Claim 1 recites a method for reducing cardiovascular disease complications in a patient following surgery comprising the step of: administering to the patient a pharmacologic cardiovascular agent prior to or during surgery, or immediately after surgery, and daily thereafter until symptoms of cardiovascular stress are reduced or the patient is discharged from the hospital wherein the agent is administered near the maximum effective dose of the agent while the patient's heart rate is greater than or equal to 65 bpm, while the patient's systolic blood pressure is greater than or equal to 100 mm Hg, and while the patient evidences no congestive heart failure, third degree heart block, or bronchospasm. The method of Claim 1 involves the administration of the pharmacologic cardiovascular agent prior to or during surgery or immediately after surgery and daily thereafter. The administration may begin prior to surgery, with the preferred timing of administration being from one day to one hour before surgery. (Page 9, lines 13-15).

Goldstein does not teach treatment with a cardiovascular agent prior to or during surgery, and the PTO incorrectly asserts that Goldstein teaches administration of atenolol immediately following cardiac-related surgery. Goldstein instead fails to teach any treatment with the study medication (nebivolol or atenolol) between surgery and a full two hours after extubation. (Page 254, col. 2). At the time of the Goldstein study (1993), bypass surgery patients were generally not extubated until the following morning after surgery. As a result patients were not extubated until up to 12 to 18 hours after surgery. Thus, administration of a β-blocking agent, according to Goldstein could occur as late as 14 to 20 hours after surgery. The delay in treatment in Goldstein is clearly in contrast to the claimed methods.

In addition, Goldstein teaches away from the claimed methods in that Goldstein teaches that all therapy for cardiovascular diseases (including β-blockers, calcium-entry blockers, vasodilators, dipyridamole and captopril) was interrupted 24 hours before surgery. (Page 254, col. 1). Again, this is in contrast to the claimed methods, wherein treatment with a β-blocking agent is given continuously, daily throughout the entire hospitalization and even after hospital discharge. (*See*, specification, for example, page 4, lines 20 to 22; page 5,

lines 23-24 and page 8, line 31 to page 9, line 6). The working example provided in the specification shows that administration of atenolol thirty-minutes prior to entering the operating room and immediately following surgery, decreased the rate of cardiac events at six months, one year and two years after surgery.

The claimed methods provide complete immediate perioperative coverage of the patient, to protect from the stresses of surgery, including extubation. Immediately following surgery, the sympathetic nervous system is active in an effort to cope with the profound assaults to the body. The increased sympathetic output results in increased heart rate and blood pressure that can cause myocardial ischemia and atherosclerotic plaque instability. Immediate perioperative coverage of the patient with an agent that reduces sympathetic effects on the cardiovascular system are not taught or suggested by Goldstein.

Kataria does not cure the defects of Goldstein because Kataria also fails to teach or suggest use of a β-blocker during surgery or immediately after surgery. Rather, Kataria teaches the use of esmolol in hypertensive postoperative patients after they emerge and recover from anesthesia following general surgery. The development of postoperative hypertension in these patients indicates that the effects of sympathetic output are already being exerted on the patient. Clearly, administration of a β-blocker after cardiovascular stresses are observed, is far too late.

Therefore, Goldstein and Kataria, alone or in combination, fail to teach or suggest each and every element of the rejected claims. Goldstein does not teach or suggest therapy with a cardiovascular agent immediately following surgery, but rather therapy that begins after extubation, which at the time of Goldstein was routinely about 12 to 18 hours after surgery. In addition, Goldstein teaches away from the claimed methods by the discontinuation of cardiovascular agents prior to surgery. Kataria also does not teach or suggest therapy with a cardiovascular agent immediately following surgery but rather teaches the treatment of a postoperative adverse event after presentation; that is, after the sympathetic nervous system affects have manifested. Applicants respectfully submit that Claims 1-6, 13-16, 49-51 and 53-55 meet the requirements for patentability and respectfully request that the rejection under 35 U.S.C. §103 be withdrawn.

CONCLUSION

Applicant submits that Claims 1-6, 13-16, 49-51 and 53-55 meet all of the criteria for patentability and are in condition for allowance. An early indication of the same and passage of Claims 1-6, 13-16, 49-51 and 53-55 to issuance is therefore kindly solicited.

The Commissioner is authorized to charge the required fee and any underpayment or credit any overpayment to the Pennie & Edmonds LLP deposit account No. 16-1150.

Respectfully submitted,

Date: January 13, 2003

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Rahul Pathak (Reg. No.)

For: Samuel B. Abrams (Reg. No. 30,605)
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090